Pediatric Endocrinology

Notes on Some Recent Advances

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• *Until recently, congenital adrenocortical hyperplasia has defied most medical and surgical therapeutic efforts. However, in properly selected patients, cortisone will suppress the abnormal cortical hormone production. This, in turn, will lead to previously inhibited maturation and developmental progress.*

Adrenocortical insufficiency calls for much diagnostic alertness, as early recognition and immediate treatment are of paramount importance. The available therapeutic means are beneficial, although their limitations and potential dangers should be heeded.

Among newly developed diagnostic techniques, thyrograms promise to be helpful in the study of thyroid hyperplasia and neoplasia. Thyroid cancer, occurring infrequently in childhood, should at the earliest possible time be treated surgically and with postoperative radiation therapy.

THE REMARKABLE PROGRESS of endocrine investigation with its impact on clinical medicine has opened new vistas and illuminated new problems. A few of the recent advances, of importance in both diagnosis and therapy, should be of especial interest to clinicians who deal with infants, children and adolescents.

CONGENITAL ADRENAL HYPERPLASIA

The studies of Wilkins and co-workers[2, 26-32] focused a great deal of attention upon congenital adrenal hyperplasia, an entity of clinical, embryological, developmental, social, psychological and pathological import. The more than occasional familial incidence of the condition is well known.[13] In females the clinical manifestations are pseudohermaphrodism and virilism; in males, macrogenitosomia praecox. The accelerated growth, muscular development and epiphyseal ossification, the early growth of puberal hair, and the progressive virilization are due to excessive secretion of adrenocortical androgens.

This abnormal production of androgens may be the only pathophysiological aberration. However, not infrequently it is associated with disturbed electrolyte regulation typical of Addison's disease, a complication leading to early death unless immediately and properly treated. An occasional patient with congenital adrenal hyperplasia will have hypertension. Very rarely the condition may be associated with signs of deficient regulation of carbohydrate metabolism.[25, 29]

Surgical and hormonal therapy (except with cortisone) of congenital adrenal hyperplasia has been disappointing. However, cortisone in proper dosage and administered at an optimal time will at least diminish the manifestations of androgenic overproduction (acne, hirsutism). In older girls it will permit the inhibited normal maturation processes to take their physiological course, as evidenced by breast development, vaginal estrinization, menarche and menstruation and adolescent feminine features and configuration. Somatic growth and development proceed equally well in boys, and in the older ones testicular maturation takes place. Early treatment with cortisone will prevent epiphyseal closure and stunting. The psychological and social benefits derived from the treatment are of importance in the adjustment of these patients to their surroundings. During cortisone administration a significant decrease in the urinary content of 17-ketosteroids and estroids takes place.

The congenitally hyperplastic cortices in all probability secrete abnormally large amounts of both androgens and estrogens. The latter have no discernible effect on females, as they are blocked by the even larger amounts of androgen. Both cortical androgens and estrogens will inhibit the secretion of pituitary gonadotropins, an interference which explains the gonadal immaturity.

The mechanism of action of the exogenous cortisone is thought to be an inhibition of pituitary production of adrenocorticotropin, causing a decrease of adrenocortical activity and permitting the release

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of pituitary gonadotropins which, at the proper time, lead to gonadal maturation and unopposed normal secondary sex development.[28] The anomalies that were present at the start are, of course, not influenced by cortisone therapy.[12]

For the initial treatment (leading to maximal suppression of 17-ketosteroid excretion in about 5 to 10 days), Wilkins prefers intramuscular administration as the results are more predictable. Infants receive 25 mg. a day, whereas children eight years of age and older are given 50 mg. a day. The daily maintenance dose (which should be determined for each patient individually) is about 5 mg. for infants and about 25 mg. for older children. The spacing of intramuscular administration of cortisone (for example, 25 mg. every 4 days in the younger and 100 mg. every 4 days in the older group) appears to lead to therapeutic results as good as those obtained with daily administration. Due to the more transient effect of cortisone given orally, more hormone is needed when it is administered by mouth. The recommended dose for infants is 5 to 12.5 mg. a day, and for older children 50 to 75 mg. a day. It is given in two or three divided doses.

With therapeutic doses of cortisone it is apparently not possible to depress the 17-ketosteroid excretion beyond a certain level. The residual amounts of urinary steroids may possibly represent metabolic end-products of the exogenous cortisone. Attempt should be made to reduce the urinary ketosteroid level below 8 mg. a day. In order to avoid toxic effects of cortisone, it is desirable to use the smallest dose that will maintain the suppression of the abnormal adrenocortical activity. The determination of this maintenance dose should be guided in the individual patient by clinical observations as well as repeated determinations of urinary 17-ketosteroid content.

It is of considerable interest that cessation of long-continued cortisone treatment is followed by an increase of urinary ketosteroids, not, however, to the pretreatment level. This may mean that the cortisone-induced suppression of adrenocortical activity persists to some extent after administration of cortisone is stopped. Whether a still longer period of treatment might result in a greater or even permanent inhibition of the cortical overactivity is not known as yet. At any rate, it appears that an infant or child with congenital adrenal hyperplasia is in need of cortisone therapy for a long period to obtain the desired benefits.

In the few reported cases of patients with hypertension coexistent with congenital adrenal hyperplasia who were treated with cortisone, good response was noted: The blood pressure remained normal for as long as a two-year period of therapy.[19, 20, 29]

The recognition and immediate treatment of hypoadrenocorticism, a not very common disorder in the pediatric age range, are of paramount importance.[4, 8, 11, 17]

Particularly in the very young, the manifestations of cortical insufficiency are easily mistaken for those of other disorders, among them pyloric stenosis, enteritis and cardiac disease.[14] The clinical signs include: vomiting, which may be projectile; visible peristaltic patterning in some infants; dehydration; diarrhea; acidosis; anorexia; loss of weight or poor gain in weight; microcardia; increasing weakness; circulatory collapse. The content of sodium, chloride and carbon dioxide in the serum is less than normal; of potassium and nonprotein nitrogen, more than normal. The eosinophil response is abnormal. Eosinophilia may be manifest in peripheral blood. The hypoglycemia and pigmentation that are characteristic of Addison's disease in older children and adults may be absent in the disease during early life.

Rarely occurring in "pure" form, the disease is more commonly associated with congenital adrenal hyperplasia. Signs of the latter or the appearance of abnormal sex manifestations in early life should warn of the possibility of incipient adrenocortical failure. Whether or not associated with another disorder, cortical insufficiency necessitates immediate action. In undiagnosed cases a clue to the underlying disorder may be given by the dramatic response to saline administration. In a number of cases the patients are known to have averted cortical failure, at least temporarily, by eating salt.

The therapeutic armamentarium for patients with cortical insufficiency includes cortical extracts, sodium chloride, cortisone and DOCA (desoxycorticosterone acetate).[2, 22] In "mixed adrenal disease," the administration of cortisone for the suppression of cortical overactivity should be undertaken with the consideration that cortisone is known to alter the requirements for DOCA. As to DOCA, it may, after a period of initial regulation, be administered in the form of pellets. Stress of one kind or another, including intercurrent infections, may necessitate a readjustment of therapeutic agents. The significant metabolic and toxic effects of excessive amounts of DOCA and cortisone should be constantly watched for and their appearance should lead to immediate reevaluation of therapeutic regimen.

In the fervor with which these and other endocrine agents are currently used, their obvious limitations must not be overlooked nor respect for their powerful metabolic and potentially harmful effects be lessened. In this connection, it is of considerable interest that cortisone injected into pregnant mice

produced cleft palate and other congenital malformations in the young. The earlier during gestation the cortisone was administered, the more severe were the defects observed in the young.[6]

DIAGNOSTIC PROCEDURES

To the array of well-established chemical, biological, histological, hematological and physical tests available for endocrine and metabolic studies (such as electrolyte and mineral determinations, hormone excretion studies and assays, tolerance tests, eosinophil response test, and radioactive iodine uptake studies) new and promising techniques have been added.

The cortisone-induced depression of urinary ketosteroids and estrogens in patients with adrenal hyperplasia helps in the differentiation between this condition and adrenocortical neoplasms. In the presence of the latter, cortisone does not suppress the urinary steroids.[15, 24, 27] By spectrometric test[7] it is possible to distinguish between androsterone and dehydroisoandrosterone. The latter steroid is often excreted in significant amounts by patients with cortical tumors.

The determination of adrenocortical response to exogenous corticotropin is a specific hormonal test and, particularly when the hormone is intravenously administered, has proven to be reliable. It serves in the differentiation of primary and secondary adrenocortical insufficiency.[23]

Testicular biopsies may be helpful in distinguishing between true sexual precocity and adrenal "precocity."[21]

The pronounced effect of injected thyrotropic hormone on the I^{131} uptake of patients with pituitary deficiency (secondary hypothyroidism) is a means of differentiating that condition from primary hypothyroidism.[16]

Functioning thyroid tissue containing adequate amounts of I^{131} can be visualized by scanning the gland with a directional scintillation counter. The resulting "scintigram" or "thyrogram" appears to be very helpful in the detection and study of hyperplastic and neoplastic disorders of the thyroid gland and in the search for aberrant thyroid tissue.[1]

CANCER OF THE THYROID GLAND

Thyroid cancer in children is rare.[9] Duffy and Fitzgerald,[5] reporting upon 28 cases in patients between 4 and 18 years of age, noted that these cases constituted 6.5 per cent of all cases of thyroid cancer observed at Memorial Hospital in New York. Horn and Ravdin,[10] in a study comprising 22 patients 25 years of age or younger, reported that those cases made up 13.8 per cent of all cases of thyroid cancer at the Hospital of the University of Pennsylvania.

The disease ordinarily runs a somewhat more benign and protracted course in persons in the younger age groups. Frequently there are long intervals between the onset of the disease (which relatively often occurs at the time of puberty) and definite diagnosis. The incidence of metastasis to cervical lymph nodes is high. The metastatic lesions may be present for years before the primary thyroid tumor is diagnosed.

It is generally agreed that the presence of a nodular goiter or any suspicious mass in the thyroid region should be considered a potentially malignant neoplasm until proven otherwise by excision and biopsy. Dailey and Lindsay[3] said that the likelihood of malignant disease is greatest if a nodule is solitary, if there has been recent enlargement, or if there is associated vocal cord paralysis.

The series from Memorial Hospital included nine patients who in the past had received radiation treatment to the thymus. However, Duffy and Fitzgerald did not feel that they could draw valid etiological conclusions. Horn and Ravdin mentioned that none of the 22 patients in their series had a history of previous radiation therapy for thymic enlargement.

Surgical extirpation and postoperative radiation treatment should be carried out at the earliest possible time. The use of radioactive iodine has definite limitations in this condition and should be reserved for a few selected patients. Rawson, Rall and Peacock[18] expressed belief that "treatment with radioactive iodine for cancer of the thyroid which is localized to the thyroid and adjacent lymph nodes and which can be removed by competent surgeons is indefensible."

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REFERENCES

1. Bauer, F. K., Goodwin, W. E., Barrett, T. F., Libby, R. L., and Cassen, B.: Scintigrams of the thyroid gland. Calif. Med., 77:380, Dec. 1952.

2. Crigler, J. F., Jr., Silverman, S. H., and Wilkins, L.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone. IV. Effect of cortisone and compound B in infants with disturbed electrolyte metabolism, Pediatrics, 10:397, Oct. 1952.

3. Dailey, M. E., and Lindsay, S.: Thyroid neoplasms in youth, J. Ped., 36:460, April 1950.

4. Deamer, W. C., and Silver, H. K.: Abnormalities in the secretion of the adrenal cortex during early life, J. Ped., 37:490, Oct. 1950.

5. Duffy, B. J., and Fitzgerald, P. J.: Cancer of the thyroid in children: a report of 28 cases, J. Clin. Endoc., 10:1296, Oct. 1950.

6. Fraser, F. C., and Fainstat, T. D.: Production of congenital defects in the offspring of pregnant mice treated with cortisone, Pediatrics, 8:527, Oct. 1951.

7. Gardner, L. I.: Diagnosis of adrenocortical tumors: a useful chemical test, Am. J. Dis. Child., 82:241, Aug. 1951.

8. Geppert, L. J., Spencer, W. A., and Richmond, A. M.: Adrenal insufficiency in infancy, J. Ped., 37:1, July 1950.

9. Hare, H. F., and Newcomb, R. V.: Carcinoma of the thyroid in children, Radiology, 54:401, March 1950.

10. Horn, R. C., Jr., and Ravdin, I. S.: Carcinoma of the thyroid gland in youth, J. Clin. Endoc., 11:1166, Oct. 1951.

11. Jaudon, J. C.: Further observations concerning hypofunction of the adrenals during early life, J. Ped., 32:641, June 1948.

12. Kelley, V. C., Ely, R. S., and Raile, R. B.: Metabolic studies in patients with congenital adrenal hyperplasia. Effects of cortisone therapy, J. Clin. Endoc. and Metab., 12:1140, Sept. 1952.

13. Knudson, A. G., Jr.: Mixed adrenal disease of infancy, J. Ped., 39:408, Oct. 1951.

14. Kyle, L. H., and Knop, C. Q.: Simulation of cardiac disease by adrenocortical failure in infants, N.E.J.M., 243: 681, Nov. 2, 1950.

15. Migeon, C. J., and Gardner, L. I.: Urinary estrogens (measured fluorometrically and biologically) in hyperadrenocorticism: Influence of cortisone, compound F, compound B and ACTH, J. Clin. Endoc. and Metab., 12:1513, Dec. 1952.

16. Pickering, D. E., and Miller, E. R.: Thyrotropic hormone in infants and children, Am. J. Dis. Child., 85:135, Feb. 1953.

17. Provenzano, R. W.: Adrenocortical hypoplasia in the newborn infant, N.E.J.M., 242:87, Jan. 19, 1950.

18. Rawson, R. W., Rall, J. E., and Peacock, W.: Limitations and indications in the treatment of cancer of the thyroid with radioactive iodine, J. Clin. Endoc., 11:1128, Oct. 1951.

19. Shepard, T. H., and Clausen, S. W.: Case of adrenogenital syndrome with hypertension treated with cortisone, Pediatrics, 8:805, Dec. 1951.

20. Shepard, T. H., and Clausen, S. W.: Hypertension in the adrenogenital syndrome treated with cortisone, Am. J. Dis. Child., 83:262, Feb. 1952.

21. Sobel, E. H., Sniffen, R. C., and Talbot, N. B.: The testis. V. Use of testicular biopsies in the differential diagnosis of precocious puberty, Pediatrics, 8:701, Nov. 1951.

22. Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D.: Functional Endocrinology from Birth Through Adolescence, Harvard University Press, 1952.

23. Thorn, G. W.: Measurement of adrenal cortical function, J. Clin. Endoc. and Metab., 13:614, May 1953.

24. Venning, E. H., Pattee, C. J., McCall, F., and Browne, J. S. L.: Effect of cortisone on the excretion of 17-ketosteroids in adrenal tumor, J. Clin. Endoc. and Metab., 12:1409, Nov. 1952.

25. White, F. P., and Sutton, L. E.: Adrenogenital syndrome with associated episodes of hypoglycemia, J. Clin. Endoc., 11:1395, Nov. 1951.

26. Wilkins, L.: Treatment of congenital adrenal hyperplasia with cortisone, Pediatrics, 9:338, March 1952.

27. Wilkins, L.: The diagnosis of the adrenogenital syndrome and its treatment with cortisone, J. Ped., 41:860, Dec. 1952.

28. Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone. II. The effects of cortisone on sexual and somatic development with an hypothesis concerning the mechanism of feminization, J. Clin. Endoc. and Metab., 12:277, March 1952.

29. Wilkins, L., Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone. III. The control of hypertension with cortisone, with a discussion of variations in the type of congenital adrenal hyperplasia and report of a case with probable defect of carbohydrate-regulating hormones, J. Clin. Endoc. and Metab., 12:1015, Aug. 1952.

30. Wilkins, L., Gardner, L. I., Crigler, J. F., Jr., Silverman, S. H., and Migeon, C. J.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone: I. Comparison of oral and intramuscular administration of cortisone, with a note on the suppressive action of compounds F and B on the adrenal, J. Clin. Endoc. and Metab., 12:257, March 1952.

31. Wilkins, L., Lewis, R. A., Klein, R., Gardner, L. I., Crigler, J. F., Jr., Rosemberg, E., and Migeon, C. J.: Treatment of congenital adrenal hyperplasia with cortisone, J. Clin. Endoc., 11:1, Jan. 1951.

32. Wilkins, L., Silverman, S. H., Crigler, J. F., Jr., Gardner, L. I., and Migeon, C. J.: Effects of long-continued treatment with cortisone in patients with congenital adrenal hyperplasia, Am. J. Dis. Child., 84:484, Oct. 1952.

No Conclusions by FDA on Boric Acid

THE FOOD AND DRUG ADMINISTRATION is investigating the use of boric acid in infants' preparations, but has come to no conclusions, according to Associate Commissioner John L. Harvey. He said there was no plan to restrict distribution. Mr. Harvey said FDA was reappraising the subject of boric acid toxicity, and when all the facts are in, "hopes to be in a position to determine whether there is any necessity for label changes or other steps in order to adequately protect the public interest." He said information was being obtained from pediatricians and other medical practitioners, as well as from sources from which "special studies of a controlled and reliable character" may be obtained.

—A.M.A. Washington Letter